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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,473	11/21/2003	Ying-Fei Wei	PF220C1	7061
22195 7590 01/04/2007 HUMAN GENOME SCIENCES INC. INTELLECTUAL PROPERTY DEPT. 14200 SHADY GROVE ROAD ROCKVILLE, MD 20850			EXAMINER SPECTOR, LORRAINE	
			ART UNIT	PAPER NUMBER
			1647	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		01/04/2007	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

10/717,473

Applicant(s)

WEI, YING-FEI

Examiner

Lorraine Spector, Ph.D.

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 16 October 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 36 and 45-71 is/are pending in the application.
- 4a) Of the above claim(s) 36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 45-71 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☒ Claim(s) 36 and 45-71 are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/16/2006</u> . | 6) <input type="checkbox"/> Other: _____  |

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of Invention II, now represented by claims 45-71 in the reply filed on 10/16/2006 is acknowledged. The traversal is on the ground(s) that the search for Inventions II and III would be overlapping. This is not found persuasive because antibodies require separate sequence search from the search for the protein itself, which search must include search for similar epitopes that may occur in unrelated proteins. Accordingly, the searches for antibody and protein are not coextensive, and would constitute an undue burden on the USPTO. It is noted that the traversal addresses additional inventions. However, all claims to said inventions having been cancelled, this additional traversal is moot and will not be further addressed.

The requirement is still deemed proper and is therefore made FINAL.

### *Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph*

Claims 45-71 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The specification disclose a nucleic acid having SEQ ID NO: 1, which is stated to encode a protein of SEQ ID NO: 2. The protein of SEQ ID NO: 2 is designated TGF $\alpha$ HIII, and is stated to belong to the EGF/TGF $\alpha$  family of cytokines. The specification discloses that the identification of TGF~ Hill was made on the basis of amino acid sequence homology to human TGF $\alpha$  (page 4 lines 1-2), however no indication of a degree of homology nor any alignment to such are provided, and a sequence search of the amino acid sequence databases did not reveal any significant homology to such (i.e. none of the 'hits' returned was an alignment with TGF $\alpha$  ). At page 6 of the specification, the sequence of the putative protein is analyzed, specifically that the protein is 229 amino acids in length, has 'significant' homology to TGF $\alpha$ , amphiregulin and cripto, and retains the six conserved cysteine residues of the EGF protein family. It is stated that residues 1-25 are a putative signal sequence which aids in secretion of the protein from the cell, that amino acids 126-177 are the 'active site' of the protein, that residues 178-204 are a transmembrane domain that may also be cleaved from

the polypeptide such as the "putative soluble portion of the polypeptide of the present invention comprises amino acid through amino acid 177 of SEQ ID NO: 2." The specification further states (page 7) that the protein exhibits the highest degree of homology to TGF $\alpha$ , although what that degree is is not disclosed.

The disclosed use for the claimed polynucleotides are for the production of the encoded protein. In cases wherein a nucleic acid is disclosed for such use, the use of the end product, the protein itself, must be considered in determining utility of the claimed nucleic acids. Disclosed uses for the encoded protein are "as research reagents and materials for discovery of treatments and diagnostics for human disease" (page 19), "for characterization of receptors" (page 19), for "restoration or enhancement of neurological functions diminished as a result of trauma or other damaging pathologies" based on the "widespread distribution of TGF $\alpha$  in various regions of the brain "suggesting that TGF $\alpha$  might play a physiological role in brain tissues" (page 20), to treat ocular disorders based on the implication of members of the TGF $\beta$  gene family in such pathologies (page 20), as toxin fusion proteins (page 21), to treat kidney disorders (page 21, based on expression of "these growth factors", presumably TGF $\alpha$ , in kidney), for treatment of liver dysfunction or for regeneration of such based on activity of TGF $\alpha$ , for wound healing, differentiation of cells (page 23), etc.

These disclosures of utility do not meet the requirements of 35 U.S.C. § 101. The disclosed utilities fall into two general classes: (a) use as research reagents for discovery of treatments diagnostics and receptors, and (b) uses based on the projection that TGF $\alpha$ HIII will have similar activity to TGF $\alpha$ , wherein possible uses are predicated on the activity or expression distribution of TGF $\alpha$ . The use as research reagents for discovery of treatments diagnostics and receptors is a use for further research only, and is not sufficient to meet the requirements of 35 U.S.C. § 101. There are no disclosed conditions which can be treated or diagnosed, such that use for such is not a readily available use, and is neither specific nor substantial in the absence of such conditions. The use to find receptors for the protein is clearly a use for further research to find out more about the protein and its properties, and does not constitute a readily available use within the meaning of 35 U.S.C. § 101.

The uses based on the expression patterns or activity of TGF $\alpha$  are not substantial. They are based on the assumption that TGF $\alpha$ HIII would have equivalent activity and expression

patterns to TGF $\alpha$ , which is not a credible assertion. van Zoelen et al., in a chapter in "Growth Factors and Receptors", teach that EGF and TGF $\alpha$  are only 40%, but they bind the same receptor, and that such binding seems to require only a certain conformation; however, they also teach that mutations at residue 47 of EGF do not perturb three-dimensional structure, but result in EGF fully lacking biological activity, suggesting that "specific conformation of these growth factors is essential, but not sufficient for high affinity receptor binding" (page 87). van Zoelen et al. also teach that there are six known ligands for the EGF receptor, which have different properties, for example the transmembrane precursor form of HB-EGF has been shown to serve as the cellular target site for the diphtheria toxin (page 86). Further, they teach that there are three additional ligands for EGFR encoded by pox viruses, which share the overall structure of EGF and TGF $\alpha$ , including the spacing of the conserved cysteine residues, and that there is a family of proteins with a "so-called 'EGF like domain'", which "share the cysteine spacing with EGF receptor ligands, but lack amino acids essential for receptor binding, and as a consequence they do not interact with the EGFR." (Page 86).

In view of the teachings in the art that (a) EGF family proteins are not highly conserved at the amino acid level, (b) that conservation of the six cysteine residues is not sufficient to indicate EGF receptor binding activity, and (c) that proteins that share the general structure of the EGF family of proteins are known which do not bind the EGF receptor, the assertion that TGF $\alpha$ HIII will bind the EGF receptor and thus have EGF/TGF $\alpha$  activity is not credible, and therefore the assertion of utility is insubstantial. Pimentel, in the Handbook of Growth Factors, vol. II. "Peptide Growth Factors (1994) teaches that there are other types of TGF's in addition to TGF $\alpha$  and TGF-beta. Pimentel discusses several different proteins which are classified as being TGF related, but each of which has different properties and functions (see pages 294-295). Therefore, the art does not support the assertion that merely because a protein has some (unspecified) degree of identity to EGF or TGF $\alpha$  and retains the six conserved cysteines that the protein can be accurately predicted to bind the EGF receptor or have a specific type of biological activity.

Accordingly, the assertion that, based solely on amino acid sequence analysis, TGF $\alpha$ HIII can be used for the same purposes as TGF $\alpha$  is not substantial.

In *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct., 1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a polynucleotide encoding a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as protein or the polynucleotides encoding it, the claimed invention is incomplete.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility for reasons asserted above, one skilled in the art clearly would not know how to use the claimed invention.

Even if the specification were enabling of a protein comprising SEQ ID NO: 2 or recited portion thereof, enablement would not be commensurate in scope with the claims, which include variant polypeptides that are 90% identical to SEQ ID NO: 2, and which are not required to have any particular activity. The specification merely discloses the nucleic acid of SEQ ID NO: 1, which is stated to encode SEQ ID NO: 2; no specific variants are disclosed, nor is there guidance as to how to make variants which retain biological activity, nor how to use variants which do not retain such activity.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level

of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In this case, although proteins that bind and activate EGF receptors were known in the art, and the relative skill in the art of molecular biology is high, the predictability in the art of altering proteins and retaining function is relatively low, especially where, as in this case, the members of the protein family that bind EGF receptors have a low degree of conservation of amino acid sequences. Taken with the lack of working examples, the lack of direction or guidance as to alterations that could be made, and the breadth of the claims, the specification fails to provide enablement commensurate in scope with the claims, even if enablement were found for the protein of SEQ ID NO: 2.

The deposit of biological organisms, specifically ATCC deposit 97342 is required for the enablement of the claims, and is acknowledged.

***Claim Rejections - 35 USC § 112, second paragraph***

Claims 56, 67, 69 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 56, 67 and 71 are indefinite as the meaning of the phrase "expressing ....by a cell" is not clear. It is not clear what method steps are intended.

Claim 69 is indefinite because it does not provide for the heterologous amino acid sequence required by claim 68, from which it depends.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 68-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Genbank accession number HO2975 or Genbank Accession number H71660, both cited by applicants.

Genbank Accession number HO2975 is an est (expressed sequence tag) clone obtained from human placenta. The clone was disclosed as being in vector pT7T3D, which is an expression vector, and in host cells DH10B. The clone has 97.2% identity to the region of bases 364-816 of SEQ ID NO: 1, including complete identity in the region of bases 380-535, as claimed in claim 21; see attached alignment.

Genbank Accession number H71660 is an est (expressed sequence tag) clone obtained from human fetal liver spleen. The clone was disclosed as being in vector pT7T3D, which is an expression vector, and in host cells DH10B. The clone has 96.9% identity to the region of bases 382-868 of SEQ ID NO: 1, see attached alignment.

The instant claims differ from the disclosures of the Genbank clones in that the Genbank disclosures do not make reference to expression of the protein encoded by the clone. However, it is noted that the clones disclosed in Genbank were contained in expression vectors, which are vectors which contain sequences necessary for the production of protein from the nucleic acid inserted into those vectors. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to express protein encoded by the inserts in either clone H71660 or HO2975 to obtain said proteins for further study, or for the production of antibodies to said proteins, such antibodies to be used to isolate the protein itself, or for immunoassay. To express such proteins is old and well known in the art, and indeed represents the use of the expression vector into which the cDNA inserts were cloned for its known and expected properties.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.



P.G. Farnham et al., Cell Growth and Differentiation 1:179, cited by applicants, discloses a DNA which is 80.1% identical to bases 587-732 of SEQ ID NO: 1.

WO 94 01548 discloses various clones, including Q77149, Q77032, Q77128 and Q77053, which have identity with the region from bases 667-900 of SEQ ID NO: 1. The publication further discloses that it is generally useful to place an expressed sequence tag (EST, a sequence isolated by virtue of being transcribed in vivo, and isolated by means of cDNA synthesis) into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such EST's. See pages 8-13.

WO 95 14772, cited by applicants, discloses sequence T21961, which is 97.3% identical to bases 722-902 of SEQ ID NO: 1. The publication is in excess of 2,000 pages, and was not available at the time this Office Action was written.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to **571-273-0893**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, reading "Lorraine Spector". The signature is fluid and cursive, with a large initial "L" and a long, sweeping underline.

Lorraine Spector, Ph.D.  
Primary Examiner



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 1 (bases 1 to 497)  
 Hillier, L., Clark, N., Dubuque, T., Elliston, K., Hawkins, M.,  
 Holman, M., Hultman, M., Kucaba, T., Le, M., Lennon, G., Marra, F.,  
 Parsons, J., Rifkin, L., Rohlfing, T., Soares, M., Tan, F.,  
 Trevasakis, E., Waterston, R., Williamson, A., Wohlmann, P. and  
 Wilson, R.  
 The Washu-Merck EST Project  
 Unpublished (1995)

TITLE JOURNAL  
 COMMENT Unpublished (1995)

REFERENCE  
 AUTHORS  
 ORGANISM  
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 Trevasakis, E., Waterston, R., Williamson, A., Wohlmann, P. and  
 Wilson, R.  
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 Vertebrata; Eutheria; Primates; Catarrhini; Hominiidae; Homo;  
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 The Washu-Merck EST Project  
 Unpublished (1995)

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